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Smoking cessation intervention for reducing disease activity in chronic autoimmune inflammatory joint diseases (Protocol)

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[Intervention Protocol]

Smoking cessation intervention for reducing disease activity in chronic autoimmune inflammatory joint diseases

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To investigate the evidence for an effect of smoking cessation interventions on smoking cessation and disease activity in smokers with IJD.

BACKGROUND

Description of the condition

Chronic inflammatory joint diseases (IJD) affect approximately 1% to 2% of the population in developed countries (Scott 2010). IJDs include rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and other forms of spondyloarthritis (SpA). Joint inflammation is a common characteristic of these conditions, potentially leading to progressive joint destruction. IJDs are, however, diverse (Michelsen 2015). RA is characterized by systemic inflammation and persistent peripheral synovitis (Scott 2010). RA is classified according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria, which incorporates joint involvement, serology, acute-phase reactants and duration of symptoms (Aletaha 2010). SpA is a common name for a group of seronegative inflammatory joint disorders involving inflammation in the axial skeleton (Sieper 2009). Classification criteria for axial SpA include back pain, active sacroiliitis on MRI, HLA-B27 positivity and clinical or patient-reported characteristics, or both (Rudwaleit 2011). AS is a subgroup of axial SpA, which is defined by the presence of radiographic sacroiliac joint damage. The classification criteria for AS include these radiographic findings plus a clinical criterion: inflammatory back pain, limitation of lumbar spine motion, reduced chest expansion or combinations of these (van der Linden 1984). Finally, PsA is characterized by polyarthritis or oligoarthritis, frequent enthesitis and may involve the axial skeleton (Gladman 2015). The

CASPAR (**ClAS**sification criteria for **P**soriatic **AR**thritis) classification criteria for PsA include current psoriasis or a history of psoriasis, a family history of psoriasis, dactylitis, juxta-articular new bone formation, rheumatoid factor negativity, and nail dystrophy (Taylor 2006).

IJDs are not curable, but disease activity can often be reduced using disease modifying antirheumatic drugs (Klareskog 2004; Klareskog 2006; Masdottir 2000). However, despite advances in the medical treatment of these diseases, a large number of patients continue to experience pain, fatigue, loss of physical function and reduced quality of life (Scott 2010). Similar to diabetes, IJD is associated with a doubled risk of cardiovascular disease (CVD). Furthermore, IJD has a significant impact on society in terms of medical costs and work disability (Carr 2003). Treatment of IJDs includes disease-modifying antirheumatic drugs (DMARDS) and tumour necrosis factor inhibitors (anti-TNFs) (Gossec 2016; Jani 2014; Scott 2010). These medications aim to reduce inflammation and progression of joint damage and symptoms of inflammatory joint diseases (Gossec 2016). People with RA who smoke have a higher need for DMARDS (Westhoff 2008). A recent cohort study concluded that current and previous smokers among patients with AS had significantly poorer treatment response to anti-TNF's compared with patients with AS who had never smoked (Glintborg 2015). In recent years, medical treatment has become more effective in decreasing joint destruction (Klareskog 2004). However, as the medications are expensive, undergoing treatment may incur a substantial economic burden, both on those dependent on medical therapy and on society (Betts 2016).

Tobacco smoking is the most significant environmental risk factor for developing IJD, particularly RA and SpA (Barbhaiya 2016; Ciurea 2013; Liao 2009; Scott 2010; Tobon 2010). Furthermore, there are indications that smoking exacerbates the symptoms of IJD (Wendling 2013), and worsens the disease outcome (Chung 2012; Sokolove 2016). Smokers suffering from IJD appear to experience more pain, fatigue and poorer health-related quality of life compared to non-smokers with IJD (Bremander 2015). Smokers with AS and axial SpA also display increased radiographic progression compared to non-smokers with the same conditions (Poddubnyy 2012; Ward 2009). Furthermore, smokers have a marginally reduced bone level compared to non-smokers (Bahrami 2016), and the nitric oxide found in tobacco smoke affects bronchial circulation and may play a role in the development of arthrosclerosis (Akrawi 1997).

Smoking subsequently increases the risk of damage to many organ systems, and is related to the occurrence of several diseases, such as CVD, chronic obstructive pulmonary disease (COPD), lung cancer and a range of other smoking-related cancers (Sopori 2002). Notably, smoking increases the risk of CVD in a population that is already at increased risk of CVD due to IJD (Edwards 2010; John 2011; Scott 2010).

Description of the intervention

Due to the increased risk of CVD in people with IJD, the European League Against Rheumatism (EULAR) has published recommendations for cardiovascular risk management. Smoking cessation is one of the current recommendations (Agca 2016). In general, intensive smoking cessation interventions with several individual or group-based counselling sessions incorporating, for example, motivational interviewing or behavioural intervention and in combination with pharmacological support, increase the chances of quitting smoking in comparison to no intervention or brief advice (short information or written material) (Stead 2016). In this review, we will investigate the evidence for an effect of smoking cessation interventions, whether brief or intensive, on smoking cessation and disease activity in smokers suffering from IJD.

How the intervention might work

Smoking affects a wide range of immunological functions, including suppression of the immune system, and specifically the pulmonary immune response. Chronic inhalation of cigarette smoke alters innate and adaptive immune responses, with nicotine being the main immunosuppressive constituent (Sopori 2002). Immune function improves as early as two months after smoking cessation (Akrawi 1997). We therefore hypothesise that smokers with IJD could benefit from smoking cessation interventions. The clinical benefit may be related to an improved immune function resulting in fewer disease relapses and reduced number of flares. IJD may be compared to inflammatory bowel diseases that, like IJD, are also autoimmune diseases. Studies have shown that smoking cessation, especially among people with Crohn's disease, reduces the frequency of flares and disease intensity (Rosenfeld 2012). Contrary to this, people with colitis ulcerosis have been reported to experience increased disease activity after smoking cessation (Rudra 1989). Furthermore, a Cochrane Review from 2004 concluded that transdermal nicotine replacement therapy (NRT) reduces disease activity in patients with ulcerative colitis (McGrath 2004).

Studies have identified smoking as a risk factor for RA (Chang 2014). Smoking can cause oxidative stress in the body. Hypothetically, smoking interventions leading to cessation may reduce oxidative stress and thereby rheumatoid inflammation. Oxidative stress can be triggered by nicotine exposure (Kalpakcioglu 2007). Smoking negatively affects the innate and adaptive immune responses. Smoking intervention, if successful, may therefore improve inflammatory responses (Sopori 2002), including lowering of fibrinogen levels, C-reactive protein (CRP), pro-inflammatory cytokines, TNF-ą , IL-1 and IL-6 which are important in the pathogenesis of RA (Gibbons 2009). Furthermore, smoking cessation may impair the development of anti-CCP antibodies that have been shown to be more prevalent in smokers (Padyukov 2004). Finally, successful smoking intervention reduces the risk of a wide range of smoking-related diseases. Specifically, the reduced risk of

CVD associated with smoking cessation is highly relevant for people suffering from IJD.

In conclusion, the detrimental effects of smoking, which can worsen disease progression in people with IJD, may be counteracted by effective smoking cessation interventions. In addition, studies suggest that smokers with IJD benefit less from DMARDS than non-smokers (Ciurea 2015; Glintborg 2015; Soderlin 2012; Westhoff 2008). As these are the most effective treatment for reducing disease progression in IJD, we hypothesize that effective smoking cessation interventions could enhance treatment efficacy.

Why it is important to do this review

Smoking appears to exacerbate disease activity, pain and deterioration of health-related quality of life in people with IJD. Smoking also further increases the already elevated risk of CVD in people with RA. Together, this impacts negatively on people's well-being, ability to work and medical costs. It is therefore important to identify whether smoking cessation interventions might also benefit disease management, reduce CVD and consumption of medication, and improve quality of life in smokers with IJD. Epidemiological studies have focused on the association between smoking and arthritis, whilst only few studies have examined the direct effect of smoking cessation interventions on smoking cessation and disease activity in people with IJD. This review will contribute to the literature by providing an overview of the evidence for the effect of smoking cessation interventions in people with IJD.

OBJECTIVES

To investigate the evidence for an effect of smoking cessation interventions on smoking cessation and disease activity in smokers with IJD.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials, including quasi-randomised and cluster randomised trials.

Types of participants

Participants will be adult daily smokers diagnosed with IJD (RA, AS, SpA or PsA) according to the classification criteria for each individual diagnosis described above (Aletaha 2010; Rudwaleit 2011; Taylor 2006; van der Linden 1984).

Types of interventions

We will include any type of smoking cessation intervention: brief or intensive behavioural support as monotherapy or combined with pharmacotherapy, or pharmacotherapy alone; individual or group-directed interventions or a combination of these. The smoking cessation intervention may be provided in any modality, including person-to-person, by telephone or digitally. Pharmacotherapy may include any type of pharmaceutical aid, such as nicotine replacement therapy (NRT), nicotine receptor partial agonists e.g. varenicline, cytisine (NRPAs) and antidepressants, e.g. bupropion. We will also include smoking cessation interventions using electronic cigarettes as aids.

Eligible control interventions will include standard care (as described in included studies); no intervention; brief information about the benefits of smoking cessation without further proactive intervention; and in the case of trials of pharmacotherapy interventions, placebo or no smoking cessation medication.

Types of outcome measures

Primary outcomes

1.1. Smoking cessation; self-reported, biochemically validated or both (biochemically verified smoking cessation will be favoured over self-reported smoking cessation where both are reported), at the longest follow-up, and measured on an intention-to-treat basis. Smoking abstinence must be reported at at least six months follow-up for studies to be eligible for inclusion. When reported, we will use the strictest definition of smoking cessation, i.e. continuous over point prevalence smoking cessation.

1.2. Disease activity score at the longest follow-up. Disease activity may be measured using DAS28 (Disease Activity Score - based on 28 swollen and tender joint counts, C-reactive protein and Visual Analog Global score) for RA and PsA (Prevoo 1995); BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) (Garrett 1994); BASFI (Bath Ankylosing Spondylitis Functional Index) (Calin 1994); and ASDAS (Ankylosing Spondylitis Disease Activity Score) for AS and SpA (Lucas 2009). Minimal clinically important difference (MCID) has been reported as follows: a change of 0.6 on DAS28 (van Riel 2004), 10 mm or 22.5% on BASDAI, 7 mm or 17.5% on BASFI (Pavy 2005), and 1.1 on ASDAS (Machado 2011).

1.3. Adverse events, including serious adverse events.

Secondary outcomes

2.1. Health-related quality of life as measured in included studies at the longest follow-up.
2.2. Pain as measured in included studies at the longest follow-up.
2.3. Disability (function) as measured in included studies at the longest follow-up.
2.4. Consumption of analgesics at the longest follow-up.
2.5. Consumption of anti-rheumatic medication at the longest follow-up.
2.6. Fatigue as measured in included studies at the longest follow-up.
2.7. Incidence of cardiovascular disease as measured in included studies at the longest follow-up.
2.8. Mortality: all-cause and those specifically related to cardiovascular disease.
We will include studies if they assess at least one primary outcome.

Search methods for identification of studies

We aim to identify all relevant studies regardless of language or publication status. If we identify studies in non-English or non-Scandinavian languages we will have them translated according to appropriate guidelines (Higgins 2011).

Electronic searches

We will search the following databases for relevant trials.

- The Cochrane Tobacco Addiction Group Specialized Register.
- The Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library.
- PubMed/MEDLINE (OvidSP) (1950 to date).
- Embase (OvidSP) (1980 to date).
- PsycINFO.
- CINAHL (1980 to date).

We have drafted a search strategy in collaboration with the Information Specialist for the Cochrane Tobacco Addiction Group (see the search strategy specific to MEDLINE in Appendix 1).
We will search the following trials registers for ongoing studies:

- The US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov)
- The EU Clinical Trials Register (ClinicalTrialsRegister.eu)
- The World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

Searching other resources

We will scan the reference lists of included studies for other relevant studies. We will also search relevant rheumatology congress abstracts to identify ongoing or unpublished research. We will contact authors of eligible studies and experts in the field for potential unreported or ongoing trials.

Data collection and analysis

Selection of studies

Two authors (IKR and TT) will initially independently assess the relevance of all titles and abstracts identified through the searches. We will resolve disagreements through discussion, involving another author (SR) if necessary. Two authors (IKR and TT) will independently search reference lists. We will retrieve all potentially eligible studies identified through this process as full-text studies and IKR and TT will independently assess them for eligibility. Again, we will call upon a third author (SR) to resolve disagreements. We will note reasons for non-inclusion of studies, delete duplicate records, and link multiple reports of the same trial by study ID.

Data extraction and management

Two reviewers (IKR and TT) will independently extract data from included studies. A third reviewer (BAE) will resolve any disagreements. The reviewers will not be blinded to authors, institutions or the publication source of trials. If relevant information and data are not reported, we will contact the authors.
We will extract the following data for all included trials: authors, title, study design, date of study start, eligibility criteria, IJD diagnosis, type of smoking cessation intervention, disease activity measure, disease duration, study duration, number of participants, number of participants allocated to each arm, number of participants lost to follow-up (for each outcome), outcome data, definitions of outcomes, details of biochemical verification, smoking duration, pack years, number of previous quit attempts, socioeconomic data, assessment time points, number of participants analysed, baseline characteristics, co-morbidity, setting, age of participants, country, source of study funding, and any conflicts of interest of the author team.

Assessment of risk of bias in included studies

We will use the Cochrane 'Risk of bias' tool to assess risk of bias in randomised controlled trials (RCTs) (Higgins 2011). This entails assessing the following domains for each study: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases. In studies where blinding is possible (pharmaceutical interventions) we will use the guidelines from the Cochrane Tobacco Addiction Group. Furthermore, we will assess performance and detection bias in studies where true blinding is not possible using the same guidelines

from the Cochrane Tobacco Addiction group and the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will give each study a rating for each domain of either 'low', 'unclear' or 'high' risk of bias, and will provide relevant information from study reports to give justification for these. A summary of the ratings given will be presented in a 'Risk of bias' figure.

Measures of treatment effect

For the smoking cessation primary outcome, we will calculate risk ratios (RRs) with 95% confidence intervals (CIs) for each study. Disease activity and quality of life outcome scores derived from different scales will be standardized where possible, and standardized mean differences (SMD) with 95% CIs will be calculated for each outcome within each study. Where the same scale is used across studies, mean differences with 95% CIs will be calculated for each study. For survival analyses, we will calculate Hazard Ratios (HR) with 95% CIs. In general, we will calculate risk ratios with 95% CIs for dichotomous data (smoking cessation, consumption of analgesics and anti-rheumatic medication, mortality and adverse events) and mean difference (MD) with 95% CIs for continuous data (disease activity, health-related quality of life, pain, disability (function) and fatigue).

Unit of analysis issues

If any cluster randomised trials (cRCT) are included, we will adjust for this by calculating the appropriate inflated variance and using a generic-inverse variance method. Where the information to make such estimates is not available, we will explore the possible effect of including cRCT in a sensitivity analysis.

Dealing with missing data

Analyses will be carried out on an intention-to-treat (ITT) basis if possible, excluding deaths, and those lost to follow-up are assumed to be smokers. If the reports do not contain sufficient data for this, we will contact the authors. If ITT analyses are not possible, we will do available-case analyses, and assess the possible bias resulting from dropouts and losses to follow-up using sensitivity analyses for the primary outcomes of smoking cessation and disease activity (Higgins 2011).

Assessment of heterogeneity

We will conduct meta-analyses of study data when there does not appear to be substantial clinical or methodological heterogeneity between trials. When meta-analysis does take place statistical heterogeneity will be assessed using the inconsistency index I^2 statistic (Higgins 2003). This describes the percentage of cross-study variability in effect estimates that is due to the difference between studies, rather than sampling error (Higgins 2011). If we find values of the I^2 statistic above 50%, we will explore the potential causes of this heterogeneity in subsequent stratified analyses, and consider whether reporting pooled estimates is appropriate.

Assessment of reporting biases

If appropriate (> 10 included trials), we will assess the likelihood of reporting bias using funnel plots.

Data synthesis

We will use Review Manager 5 software (RevMan 5) to carry out any meta-analyses. We will perform a sensitivity analysis using random-effects models (Riley 2011). If possible, we will summarize effects across studies using the random-effects method. Otherwise, we will summarize effects narratively.
For the primary outcomes (smoking cessation and disease activity) we will also calculate the numbers needed to treat where possible. If there are not sufficient studies, or in the case of a large amount of clinical or methodological heterogeneity, we will summarize the results narratively rather than quantitatively.

Subgroup analysis and investigation of heterogeneity

If possible, we intend to undertake a subgroup analysis of brief versus intensive smoking cessation interventions in order to investigate any differential effects according to the intensity of the interventions. We also intend to undertake a subgroup analysis of people treated with biologic versus non-biologic DMARDS in order to explore possible differential effects of the smoking cessation intervention according to treatment received.

Sensitivity analysis

We will perform a sensitivity analysis excluding studies with a drop-out rate exceeding 20% to explore any potential impact of missing data on overall effects. Furthermore, we will perform sensitivity analyses excluding studies at high risk of bias.

Summary of findings

We will use the GRADE tool to assess the quality of the evidence for the two primary outcomes: smoking cessation and disease activity. We will do this by considering methodological quality, directness of the evidence, heterogeneity, precision of effect estimates, and risk of publication bias for each outcome (Higgins 2011). Based on the GRADE criteria, we will grade the quality of the evidence contributing to each outcome individually as very low, low, moderate or high. Two authors (TT and IKR) will independently carry out and compare GRADE assessments. We will resolve any disagreements through discussion with a third author (BAE). We will present our final judgments in a 'Summary of findings' table.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (OVID) search strategy

/ indicates MeSH term, .mp searches title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
1. smoking cessation.mp
2. exp Smoking Cessation/
3. Smoking/pc, th [Prevention & Control, Therapy]
4. Tobacco-Use-Cessation/ [MeSH]
5. Tobacco-Use-Disorder/ [MeSH]
6. ((quit$ or stop$ or ceas$ or giv$ or abstain* or abstin*) adj5 (smoking or smoke* or tobacco).ti,ab.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Arthritis, Rheumatoid/
9. rheumatoid arthritis.mp
10. exp Spondylarthropathies/ [MeSH]
11. ankylosing spondylitis.mp
12. psoriatic arthritis.mp
13. spondyloarthritis.mp
14. inflammatory arthritis.mp or inflammatory arthritides.mp
15. 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 7 and 15

WHAT'S NEW

Last assessed as up-to-date: 14 February 2018.

Date	Event	Description
21 February 2018	Amended	author name spelling correction

CONTRIBUTIONS OF AUTHORS

IKR was the contact person with the editorial base and coordinated the contributions from the co-authors.

IKR, BAE, MØ, SR, AGS, RC and TT co-wrote the protocol.

DECLARATIONS OF INTEREST

Robin Christensen: none to declare; reports being among the statistical editors of the Cochrane Musculoskeletal Group.

Bente Appel Esbensen: none to declare.

Ida Kristiane Roelsgaard: none to declare.

Silvia Rollefstad: none to declare.

Anne Grete Semb: has received consulting fees from a Cluster financed by the German government (Excellence Cluster Inflammation at Interfaces) and from industry, for lectures given to health professionals. None of these lectures or the fee for developing and giving them have been related to the present review on smoking cessation and rheumatoid arthritis. Therefore, this is not deemed as a conflict of interest. AGS has also received a grant from the South East Health Authority (2013064), which is a Norwegian government grant covering 8 years as a senior researcher at the Preventive Cardio-Rheuma clinic, Department of Rheumatology, Diakonhjemmet Hospital. This is not deemed to be a conflict of interest.

Thordis Thomsen: none to declare.

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